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Comparison of the efficacy and safety of nebulized beclometasone dipropionate and budesonide in severe persistent childhood asthma

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Abstract Inhaled steroids are recommended for long-term control of asthma, but their use may be limited in young children because of difficulties in using the associated inhaler device. The use of nebulizers may help to overcome this issue, without compromising therapeutic efficacy or safety. This 14-week, multicentre, randomized, controlled, open-label, parallel-group study compared the efficacy and safety of nebulized corticosteroids in paediatric patients (aged 6 months to 6 years) with severe persistent asthma. Beclometasone dipropionate (BDP) 800 μg day^{-1} suspension for nebulization and budesonide (BUD) 750 μg day^{-1} given by nebulization in a twice-daily regimen, and when used in addition to the usual maintenance therapy, resulted in comparable clinical efficacy across all parameters. The primary efficacy endpoint was the number of patients who did not experience any major exacerbation, this being 40·4% and 51·7% in the BDP and BUD groups respectively in the ITT population (P=0·28), and the mean number of global exacerbations (major plus minor) decreased respectively by −37.5% in the BDP group and −23.3% in the BUD group. Both treatments were also associated with marked reductions in the number of nights with wheezing and the number of days of oral steroid use. Moreover, the two treatment groups had a similar adverse-event incidence and profile. Only 11 adverse events were reported, and no serious adverse events were related to treatment. Urinary cortisol and the time course of height and weight were unaffected by both treatments, and BDP was confirmed to have a neutral effect on bone metabolism. In conclusion, this study demonstrates that both BDP 800 μg day^{-1} suspension for nebulization and BUD 750 μg day^{-1} administered by nebulization are effective, with an acceptable safety profile, for treatment of severe persistent asthma in infants and young children.

Keywords asthma; beclometasone dipropionate; budesonide; nebulized corticosteroids.

INTRODUCTION

Despite the growing knowledge of the pathogenesis of asthma, the prevalence of this disease appears to be on the increase. Indeed, asthma is now the most common chronic disease amongst children, affecting some 5–10% of children under the age of 6 years: around 10% of asthmatic children develop symptoms before the age of 1 year, and over 50% by the age of 2 years.

The prevention of long-term respiratory complications associated with asthma is based on early and adapted management of the condition, in particular by using anti-inflammatory therapy as early as possible. Furthermore, administration via inhalation is the preferred route for asthmatic children on account of its rapid action, and also its favourable safety: efficacy ratio compared with oral therapy.

In infants and young children suffering from asthma, selection of the method of delivery of medication is essentially dictated by the option that requires minimum co-operation, and during acute asthma attacks nebulization offers this advantage, especially in young dyspnoeic children. Although the introduction of metered-dose inhalers (MDIs) and dry powder inhalers (DPIs) have reduced the use of nebulized therapy, problems with hand-to-lung co-ordination and inspiratory flow are common in children. Nebulizers can overcome both the co-ordination problems associated with MDI use and the inspiratory difficulties encountered with DPIs (1,2).

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Beclometasone dipropionate (BDP) is a steroid that has been in clinical use as an inhalation anti-inflammatory treatment for asthma since the 1970s and remains the reference drug for inhaled anti-inflammatory therapy in asthma. The purpose of this study was to evaluate the efficacy and safety of BDP suspension for nebulization in treating severe asthma in infants and young children when compared with the currently available nebulized formulation of the steroid budesonide (BUD).

MATERIALS AND METHODS

Patients

A total of 130 outpatient infants or children, male and female, aged 6 months to 6 years, with severe persistent asthma were selected for participation in the study. Severe persistent asthma was defined as asthma (a history of at least three episodes of wheezing dyspnoea) associated with at least one of the following severity criteria: daily wheezing, with or without cough, for at least a fortnight before inclusion; experiencing at least one exacerbation per month requiring oral steroid therapy during the 3 months preceding inclusion in the study. Patients with an allergy to any of the constituents of the test products or concomitant therapies, presenting with other pulmonary (including cystic fibrosis, cardiopulmonary malformation, immune deficiency, and active tuberculosis) or major non-pulmonary concomitant (including non-treated gastro-oesophageal reflux, and cardiac and/or renal and/or hepatic and/or neurological disease) conditions, or taking long-acting β_2-agonists were excluded from participation in the study.

The study was approved by the Ethics Committee of Hopital Purpan, Toulouse, and was conducted according to Good Clinical Practices Guidelines.

Study design

A 14-week, multicentre, randomized, controlled, parallel-group, open-label study. Patients who met inclusion and exclusion criteria were randomized to one of two treatment arms: BDP 800 $\mu g\ day^{-1}$ b.i.d. suspension for nebulization (Clenil A®, Chiesi Farmaceutici SpA, Parma, Italy), or BUD 750 $\mu g\ day^{-1}$ b.i.d. (Pulmicort® Repsules, Astra Pharmaceuticals Ltd., Kings Langley, Herts, U.K.). Both drugs were administered using a Pari Boy Junior nebulizer (Pari GmbH, Starnberg, Germany).

Following a 2-week run-in phase with maintenance therapy of oral ketotifen 1–2 $mg\ day^{-1}$ (Zaditen®, Novartis Pharmaceuticals, Basel, Switzerland), patients were randomized to 12 weeks' treatment with either BDP or BUD, plus ketotifen.

Patients were assessed at various stages during the study: during the initial 2-week run-in period (visit 1), at 2 weeks (visit 2), and thereafter at 4-weekly intervals (visits 3–5).

Concomitant treatments permitted in the study when necessary were certain bronchodilators, oral steroids, and antibiotics. The bronchodilators authorized during the study were nebulized salbutamol, terbutaline, or ipratropium bromide, or inhaled salbutamol or terbutaline. Antihistamines other than ketotifen, inhaled steroids other than those authorized in the study, inhaled cromones, β_2-agonists other than salbutamol and terbutaline in maintenance therapy, and maintenance treatment with anticholinergics or theophyllines were excluded. Informed and written consent was obtained from the parents of the patients prior to study inclusion.

Assessments

The primary efficacy evaluation criterion in the study was the percentage of patients who did not experience at least one major exacerbation during the study treatment period (after visit 2). A major exacerbation was defined as failure in 1 hour of two nebulizations of salbutamol, terbutaline, or ipratropium bromide, or two/three inhalations of two puffs of salbutamol or terbutaline, and the need for oral steroid therapy for at least 2 consecutive days. Major secondary efficacy endpoints were the number of major plus minor exacerbations, the time to onset of the first major exacerbation, the number of nebulizations or inhalations of salbutamol, the mean duration of oral steroid therapy, the number of days and nights with wheezing and with cough, and parental absenteeism from work due to child disease. The primary safety evaluation parameter in the study was the concentration of urinary deoxypyridinoline measured by ELISA and expressed by the urinary deoxypyridinoline: urinary creatinine ratio, to determine the effect of the steroid treatments on bone resorption. Secondary safety criteria included the cortisol: creatinine ratio in the first morning urine sample, height and weight gains between visits 2 and 5, and adverse events reported by the parents. Clinical safety was assessed at each visit during the study.

Statistical analysis

Efficacy was analysed on the basis of intent-to-treat (ITT) and per protocol (PP) populations, and safety was analysed in all patients who received at least one randomized treatment unit. The primary analysis was undertaken on the ITT population.

Group comparisons for the primary efficacy endpoint involved comparison by the Chi-square test, and for secondary endpoints by the *t* test or Wilcoxon's test.

Group comparisons for primary and secondary safety criteria used two-way analysis of variance for repeated measurements. Description by body system for adverse

Table 1. Demographic data of asthmatic infants and young children selected for treatment with beclometasone dipropionate suspension for nebulization or nebulized budesonide

Demographic characteristic	Total	Beclometasone dipropionate	Budesonide
Gender:			
Male	93	43	50
Female	37	19	18
Total	130	62	68
Mean ± SD age (years)	2·1 ± 1·4	2·1 ± 1·4	2·1 ± 1·5
Mean ± SD weight (kg)	12·5 ± 3·8	12·6 ± 3·7	12·3 ± 3·8
Mean ± SD height (cm)	84·8 ± 14·3	85·1 ± 14·2	84·6 ± 14·5
Body mass index (kg m^{-2})	17·2 ± 2·0	17·2 ± 2·0	17·1 ± ·9

events and intergroup comparisons used the Chi-square test.

RESULTS

Patient population

Of the 130 patients (mean age 2·1 ± 1·4 years) screened for the study in 24 centres, 120 were randomized to treatment: 58 to BDP, and 62 to BUD. The number of major exacerbations after visit 2 was not available for three patients (one in the BDP group and two in the BUD group), who were then eliminated from the ITT population, and 18 patients (five in the BDP group and 13 in the BUD group) presented at least one major protocol violation. In total, therefore, 117 patients were analysed in the ITT population (57 treated with BDP and 60 with BUD) and 99 in the PP population (52 treated with BDP and 47 with BUD). The groups were homogeneous in terms of demographic characteristics at selection (Table 1).

Evaluation of efficacy

All results obtained from the ITT population were confirmed by those of the PP population, and consequently only ITT results are presented here.

Similar results were demonstrated for the two treatment arms for all efficacy parameters (Table 2, Figures 1–5) during the entire randomized treatment period, with no statistically significant differences noted between the groups.

Examination of the primary efficacy endpoint demonstrated that 40·4% of BDP-treated patients and 51·7% of BUD patients did not experience any exacerbations during the treatment period, with the difference between the groups being non-significant (P=0·22). The mean number of global exacerbations (major plus minor) decreased respectively by –37·5% in the BDP group and –23·3% in the BUD group. No significant differences were found between the groups (P=0·28). The mean time to onset of the first major exacerbation was 46·3 days for BDP patients vs 46·1 days for BUD patients, with no difference evident between the two groups (P=0·72) (Figure 1).

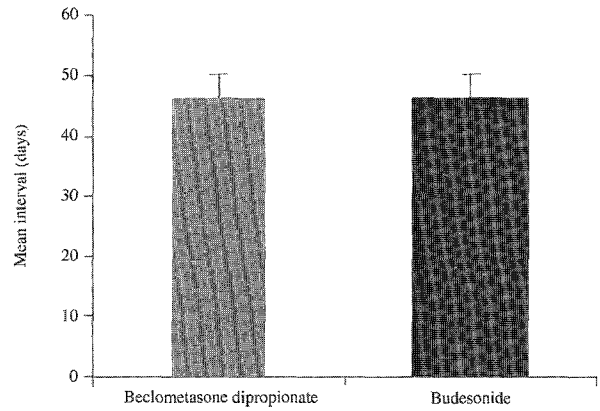

FIGURE 1. Time to onset of the first major exacerbation. ITT population.

The two treatment groups were subsequently found to have produced a significant and similar reduction in the number of exacerbations (major + minor) per patient per day between the run-in and treatment periods: down by 37·5% for the BDP group and by 23·3% for the BUD group (P=0·60) (Table 3).

Both BDP and BUD produced particularly marked effects with respect to the mean number of days of oral steroid therapy, with significant reductions of 66·7% for the BDP group (P=0·002) and 58·3% for the BUD group (P=0·007) (Figure 2). No significant differences were found between the groups for the randomized treatment period (P=0·19).

The mean number of nebulizations or inhalations of salbutamol varied significantly during the study, with significant reductions of 61.8% for the BDP group (P<0·0001) and 57·8% for the BUD group (P<0·0001), and were similar for the two groups during the treatment period (P=0·22) (Figure 3).

The mean number of days with wheezing varied significantly during the study, with significant reductions of 53·1% for the BDP group (P=0·001) and 64·3% for the

Table 2. The mean effect of beclometasone dipropionate suspension for nebulization or nebulized budesonide on various efficacy parameters in the intent-to-treat population of asthmatic infants and young children

	Visits 1–2			Visits 2–5		
Efficacy parameter	BDP (*n*=57*)	BUD (*n*=59†)	*P* value	BDP (*n*=55¶)	BUD (*n*=56**)	*P* value
Number (m ± SD) of major exacerbations	0.018 ± 0.031	0.017 ± 0.034	0.77	0.012 ± 0.014	0.009 ± 0.012	0.28
Number (m ± SD) of days of oral steroid therapy	0.15 ± 0.20	0.12 ± 0.19	0.40	0.056 ± 0.064	0.042 ± 0.055	0.19
Number (m ± SD) of minor exacerbations	0.006 ± 0.03	0.002 ± 0.01	0.41	0.0032 ± 0.0068	0.0033 ± 0.006	0.97
Number (m ± SD) of nebulizations/inhalations of salbutamol	2.20 ± 2.24	1.92 ± 1.49	0.44	1.23 ± 2.40	0.81 ± 1.01	0.22
Number (m ± SD) of days with wheezing	0.32 ± 0.37	0.28 ± 0.30	0.58	0.22 ± 0.41	0.13 ± 0.18	0.13
Number (m ± SD) of nights with wheezing	0.19 ± 0.30	0.11 ± 0.18	0.07	0.09 ± 0.16	0.03 ± 0.05	0.02
Number (m ± SD) of days with cough	0.67 ± 0.32	0.63 ± 0.33	0.55	0.46 ± 0.45	0.38 ± 0.25	0.23
Number (m ± SD) of nights with cough	0.45 ± 0.37	0.33 ± 0.32	0.07	0.28 ± 0.27	0.20 ± 0.19	0.007
Number (m ± SD) of days of parental absenteeism	0.016 ± 0.05	0.014 ± 0.05	0.82	0.016 ± 0.046	0.009 ± 0.044	0.43

BDP beclometasone dipropionate, BUD budesonide. m is the mean value of the studied variable. For each patient the variable is divided by the days of treatment, then an average is calculated for all patients, this number appears in the tables as mean. *n=56 for number of days of oral steroid therapy and school and parental absenteeism; †n=56 for number of days of oral steroid therapy, n=57 for number of days of school absenteeism, n=58 for number of days of parental absenteeism; ¶n=54 for number of days of school and parental absenteeism; **n=53 for number of days of school and parental absenteeism.

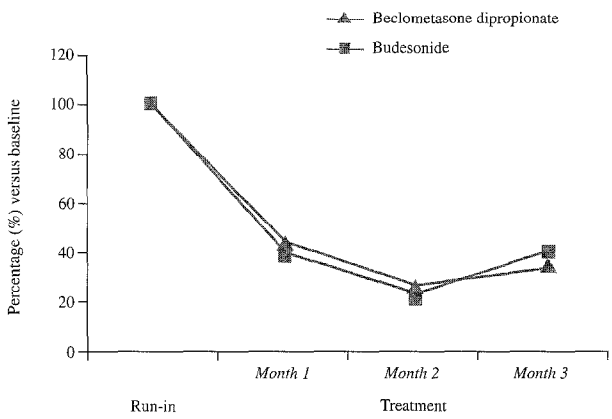

FIGURE 2. Mean number of days of oral steroid therapy in the intention-to-treat population of asthmatic infants and young children.

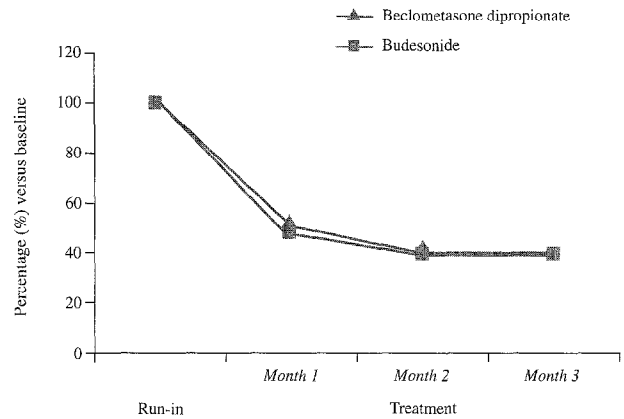

FIGURE 3. Mean number of nebulizations/inhalations of salbutamol in the intention-to-treat population of asthmatic infants and young children.

BUD group (P<0·0001) (Figure 4). No significant differences were found between the groups for the randomized treatment period (P=0·13).

The mean number of nights with wheezing during the study was notably reduced, with significant reductions of 63% for the BDP group (P=0·001) and 72·7% for the BUD group (P=0·002) (Figure 5). The difference between the two treatments was significant (P=0·02).

The mean number of days with cough varied significantly during the study, with reductions of 49·3% for the BDP group (P<0·0001) and 49·2% for the BUD group (P<0·0001). Between-group differences were non-

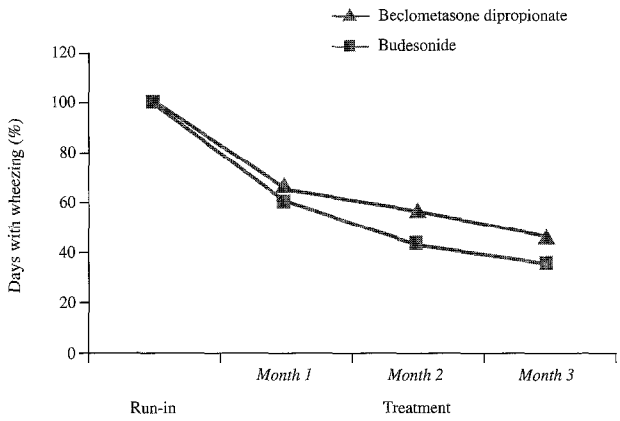

FIGURE 4. Mean number of days with wheezing in the intention-to-treat population of asthmatic infants and young children.

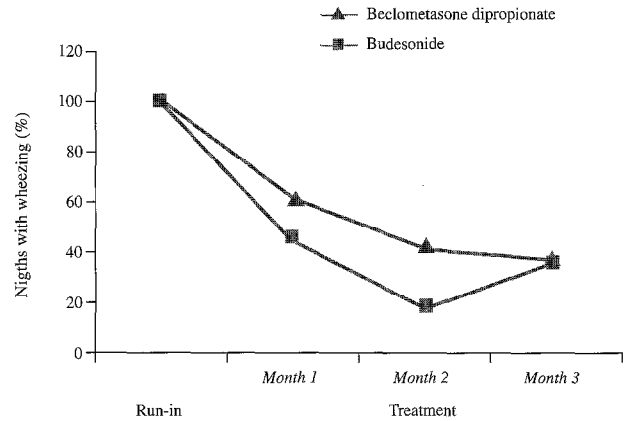

FIGURE 5. Mean number of nights with wheezing in the intention-to-treat population of asthmatic infants and young children.

Table 3. Evolution of number of exacerbations (major + minor) per day and per patient between the run-in and treatment periods in the intent-to-treat population

		Beclometasone dipropionate		Budesonide
Δ of number of exacerbations	N	57		60
	M	−0·00936		−0·00538
	SD	4·279		3·795
Percentage of decrease from baseline		−37·5%		−23·3%
P value			0·60	
Difference 95% CI			[−1·9 to 1·09]	
P value adjusted to baseline			0·72	
Difference 95% CI adjusted to baseline			[−0·18 to 0·98]	

significant for the entire randomized treatment period (P=0·23).

The mean number of nights with cough also varied considerably during the study, with significant reductions of 55·6% for the BDP group (P<0·0001) and 45·5% for the BUD group (P=0·004). No significant difference was found between the two treatments (P=0·07).

Finally, according to patient and investigator assessments of treatment, some 40–51% of patients considered treatment with either BDP or BUD to be 'good' or 'very good' at treatment end in both the ITT and PP populations.

Evaluation of safety

Assessment of clinical safety of the two treatments was based on 130 subjects. There was no change in bone metabolism, as indicated by a static urinary deoxypyridinoline : urinary creatinine ratio, for either group (Table 4). Urinary cortisol and urinary cortisol/creatinine ratios were not significantly affected during treatment for both the BDP and BUD groups (Table 5). Patients in the BDP and BUD groups also had similar increases in bodyweight and height during the study.

In total, 417 emergent adverse effects were reported during the study, 79 of which occurred in the run-in phase and 338 in the randomized treatment period. Of the 338 adverse events observed in the randomized treatment period, 168 were reported in the BDP group and 170 in the BUD group. However, only 11 adverse events in total (five in the BDP group and six in the BUD group) were considered to be treatment-related. Furthermore, none of the 16 serious adverse events reported by 14 patients during the study (eight adverse events and seven patients in each group) were found to be related to treatment. Overall, the frequency and profile of adverse events were equivalent for the two treatments, with side-effects generally being associated with the ear, nose, and throat, and respiratory system.

DISCUSSION

Inhaled steroid therapy is recommended for the long-term control of asthma in children (3). However, some

Table 4. The time course of urinary deoxypyridinoline/urinary creatinine ratio in the intention-to-treat population of asthmatic infants and young children

		V2		V5	
		BDP	BUD	BDP	BUD
Urinary deoxypyridinoline/urinary creatinine	N	56	60	47	46
	m	57·23	52·88	56·41	50·97
	SD	25·31	20·01	25·22	22·34
	Min	20·10	19·60	22·90	15·50
	Max	135·30	119·00	118·00	101·80
	Med	53·90	48·25	50·70	45·60
Missing data		6	8	15	22
P		0·31		0·27	
95% CI of the difference		[−4·02 to 12·71]		[−4·38 to 15·27]	

BDP, beclometasone dipropionate; BUD, budesonide

Table 5. The time course of urinary cortisol in the intention-to-treat population of asthmatic infants and young children

		V2		V5	
		BDP	BUD	BDP	BUD
Urinary cortisol	N	50	53	46	44
	m	64·66	78·34	91·59	120·18
	SD	50·29	93·44	76·35	327·77
	Min	9	6	5	8
	Max	223	570	376	2214
	Med	48	42	82·5	60
Values below the limit of detection (<5)		4	2	0	0
P (Wilcoxon)		0·84		0·27	

BDP, beclometasone dipropionate; BUD, budesonide

young children may experience co-ordination and/or inspiratory difficulties when using available MDIs or DPIs and in such instances nebulization may be useful since this method of administration requires minimum co-operation. Indeed, the efficacy of steroid therapy, namely BUD, given via nebulization as a basic treatment for infants and children with asthma has been confirmed in a number of studies undertaken to date (4–8).

This present study was to designed to compare the efficacy and safety of BDP suspension for nebulization with those of BUD, both given via a nebulizer as a 12-week treatment for severe persistent asthma in infants and children.

The results of the study demonstrated that nebulized forms of BDP and BUD had similar effects with regard to the various efficacy criteria assessed, which included asthma exacerbations (major and minor) and symptoms, and the use of rescue medication. The results were not biased for separation between major and minor exacerbations since no difference was demonstrated during a *post-hoc* analysis of total exacerbations. Both treatments had a particularly notable effect in reducing the number of nights of wheezing and days of oral steroid use. Furthermore, a similar adverse-event profile was reported for the two treatments.

Efficacy was primarily assessed by the incidence of major and minor exacerbations during the treatment period, analysed separately. These two parameters were defined as bronchodilator treatment failure associated with a non-planned physician visit for minor exacerbations, and bronchodilator treatment failure associated with a non-planned physician visit plus oral steroid prescription for major exacerbations. Oral steroid prescriptions are mainly dependent on physician habit and could vary significantly from one physician to another. As major and minor exacerbations differ only by the prescription of oral steroids, it was logical to pool them in a *post-hoc* analysis to explore an overall parameter termed 'non-planned physician visit' which is a very important parameter for the follow-up of asthmatic children. The results of this analysis are shown in Table 3, expressed as the number of exacerbations (major + minor) per patient per day, and confirm the initial findings – i.e. a comparable clinical effect between BDP 800 $\mu g\ day^{-1}$

b.i.d. suspension for nebulization and nebulized BUD 750 μg day^{-1} b.i.d.

There are few previous comparative studies of inhaled BDP and BUD in asthmatic children. Two double-blind, randomized, crossover trials have shown equivalent efficacy of 400 μg day^{-1} BDP and BUD (used with spacer) over 1 month, as measured by twice-daily PEFRs and recorded symptoms (9,10). In another study in 12 asthmatic children, significant improvements in lung function tests were achieved following administration of 400 μg day^{-1} BDP and BUD over 2 weeks; there was no significant difference in efficacy between the two treatments (11). In a fourth study, BUD (used with spacer) and BDP 100 μg twice-daily was administered over 3 weeks in a double-blind cross-over trial in 21 children. Morning and evening PEFR values were significantly higher with BUD; however, FEV_1 values for the two regimens were not statistically different (12).

The results of this study are consistent with those of a previous study of 127 children with mild to moderate persistent asthma aged from 6 to 14 years. The administration of BDP 800 μg day^{-1} b.i.d. suspension for nebulization and BUD 1000 μg day^{-1} b.i.d. via nebulizer produced significant and similar beneficial effects vs baseline in final mean PEFR, FEV_1, and the use of rescue medication, with acceptable safety and tolerability profiles (13).

The results of this study support the clinical use of BDP 800 μg day^{-1} suspension for nebulization for the treatment of infants and young children with severe persistent asthma. BDP suspension for nebulization is as safe and clinically effective as nebulized BUD and appears to be a suitable and valuable therapeutic alternative for asthma in this young patient population.

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